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ORIGINAL ARTICLE

Ocular Manifestations in an Italian Cohort of Patients with Takayasu Arteritis

Rosanna Dammacco, MD[a], Luca Cimino, MD[b,c], Luca De Simone, MD[c], Giovanni Alessio, MD[a], and Franco Dammacco, MD[d]

[a]Department of Ophthalmology and Neuroscience, University of Bari "Aldo Moro," Medical School, Bari, Italy; [b]Department of Surgery, Medicine, Dentistry and Morphological Sciences, Dentistry and Morphological Sciences, University of Modena and Reggio Emilia, Modena, Italy; [c]Ocular Immunology Unit, Azienda USL-IRCCS, Reggio Emilia, Italy; [d]Department of Biomedical Sciences and Human Oncology, University of Bari "Aldo Moro," Medical School, Bari, Italy

ABSTRACT

Purpose: We describe ophthalmic manifestations, therapy, and outcomes in 16 patients with Takayasu arteritis (TA).

Methods: Takayasu retinopathy was detected in 15 eyes of 9 patients and hypertensive retinopathy in 14 eyes of 7 patients.

Results: Visual acuity was normal in 7 eyes, 20/40 to 20/200 in 20 eyes, counting fingers in 2 eyes, hand motion in 2 eyes, and no light perception in 1 eye. Glucocorticoids associated with immunosuppressive agents induced a sustained remission in 13 patients. Three relapsing-refractory patients were given the monoclonal antibody tocilizumab, which led to partial and complete response in 1 and 2 patients respectively. Steroid-induced cataracts developed in 4 patients. Restenosis and the consequent recurrence of visual symptoms were detected in 2 of 9 patients who underwent a patency procedure for their stenotic lesions.

Conclusions: Ocular manifestations were a common feature (37.2%) in our cohort of TA patients and were frequently responsible for severe visual deterioration.

Abbreviations: BCVA: best-corrected visual acuity; FFA: fundus fluorescein angiography; GC: glucocorticoids; HR: hypertensive retinopathy; ITAS: Indian Takayasu activity score; OCT: optical coherence tomography; TA: Takayasu arteritis; TR: Takayasu retinopathy.

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Takayasu arteritis (TA) is a systemic, granulomatous, large-vessel vasculitis of unknown etiology, involving the aorta and its major branches as well as the subclavian, carotid, and renal arteries to a variable extent.[1–5] The disease occurs, usually but not exclusively, before the age of 50 years and thus differs from giant cell arteritis, whose onset is by far more frequent after age 50.[6] Although TA has long been considered a rare disease, with a higher prevalence in women of child-bearing age living in Asia, the extensive adoption of non-invasive imaging techniques has led to the diagnosis of TA in patients of all ethnicities worldwide.[7–10]

The clinical course of TA may be extremely heterogeneous and insidious. This is especially the case in the early phases of the disorder, which are characterized by constitutional and other non-specific signs and symptoms that make a correct diagnosis challenging. Several weeks or months after disease onset, a definite diagnosis can be made based on the development of ischemic and/or hypertensive symptoms resulting from stenosis or aneurysms of the aorta and its main branches, together with imaging findings. Detailed accounts of the clinical features of TA, the possible pathogenetic mechanisms, and the conventional, biological, and surgical (recanalization) approaches to therapy can be found in excellent reviews[3,10–12] and in a publication by our group based on our own clinical experience.[13]

Remarkably protean ocular manifestations have been described in several case reports[14–21] and a few retrospective case series[22–24] of TA. Their prevalence, not easy to establish given the relative rarity of TA, seems to range from transient or stable vision loss in 4–8% of patients to retinal vasculitis in 14–15%, possibly reflecting geographic, genetic, and diagnostic factors.[10] An ocular ischemic syndrome, mostly bilateral, may be the presenting manifestation of TA or develop at any stage of the disease. In both situations, an early diagnosis and the subsequent implementation of a recanalization procedure may protect visual function or lead to its recovery. Thus, in the multidisciplinary management strategy of TA patients, the ophthalmologist plays an indispensable role.

In the following, we describe the ophthalmic manifestations, therapeutic measures, and outcomes in a cohort of Italian TA patients residing in the Apulia region of Italy.

Material and methods

This retrospective, observational study was carried out on an initial series of 43 patients diagnosed with TA from 2003 to 2018. All patients were examined in two tertiary referral centers of the University of Bari Medical School that have specific experience in ophthalmology and clinical immunology,

CONTACT Franco Dammacco francesco.dammacco@uniba.it Department of Biomedical Sciences and Human Oncology, University of Bari "Aldo Moro" Medical School, Polyclinic, Piazza Giulio Cesare, 11, 70124, Italy

respectively. In addition, to provide a comprehensive description of the ophthalmic presentations of TA, a collaboration was conducted with the Ocular Immunology Unit, Reggio Emilia Hospital, Italy. This institution contributed to the design and interpretation of the study and provided representative images of Takayasu retinopathy. All procedures conformed to the tenets of the 1964 Helsinki Declaration and its later amendments. The University of Bari Ethics Committee approved the study and, based on the design of the study as a retrospective case record review, waived the need for the patients' written informed consent to study enrollment.

A female patient with severe hypertension was incidentally found to have exudative retinal detachment and papilledema while being assessed at the ophthalmology clinic of our university. She then underwent a full examination in the Department of Internal Medicine of the same university, which led to the diagnosis of TA. The remaining 42 patients were first diagnosed with TA by internists and then referred for a thorough ophthalmologic assessment, independent of whether they complained of ocular symptoms. At variable times during the course of the disease, 15 of these patients developed ocular involvement.

TA was diagnosed according to the American College of Rheumatology classification criteria published in 1990 and summarized in Table 1 [25] In addition, based on the angiographic detection of vascular areas involved by the arteritic process, each patient was assigned to one of five groups defined by the TA type.[26–28] In type I, the aortic arch and its major branches are involved. Type II is subdivided into subtype IIa when the lesions affect the ascending aorta, aortic arch, and its branches, and subtype IIb when the thoracic descending aorta is involved, with or without involvement of the ascending aorta or the aortic arch and its branches. In type III, both the descending thoracic aorta and the abdominal aorta, plus or minus the renal arteries, are affected. Type IV refers to the involvement of the abdominal aorta and/or the renal arteries. In type V, the inflammatory process involves the entire aorta and its branches. The additional designation C(+) or P(+) identifies patients in whom the coronary or pulmonary arteries are also affected.[27,28]

The different clinical phases of TA were defined as described elsewhere.[8,29] Briefly, active disease consisted of the presence of at least two of the following criteria: i) systemic signs or symptoms not ascribable to other conditions; ii) erythrocyte sedimentation rate > 30 mm/hr or a C-reactive protein level > 8 mg/L in the absence of infection or malignant tumors; iii) the detection of signs or symptoms of vascular insufficiency; iv) the detection of new vascular lesion(s) on imaging studies. The remission phase was defined as the regression of clinical and laboratory indicators of active disease, in the absence of new vascular lesions detected on sequential imaging studies. Remission was considered sustained when the criteria for remission were met for at least 6 months in patients receiving < 10 mg prednisone/day. Relapse was defined as the reappearance of signs and symptoms of active disease after an undefined period of remission.

All patients underwent a thorough ophthalmologic examination, including best corrected visual acuity (BCVA), slit-lamp biomicroscopy, pupillary reaction, ocular motility, visual field testing, external inspection, spectral domain optical coherence tomography (OCT), direct ophthalmoscopy, and fundus fluorescein angiography (FFA), which is commonly considered as the gold standard for the diagnosis of TA.[10] OCT angiography was performed in 9 patients. Additional tests were carried out as requested, both at the time of diagnosis and at variable intervals during follow-up.

Takayasu retinopathy (TR), characterized by chronic ischemia, was staged according to the classification system of Uyama and Asayama[30]: stage 1) dilation of retinal veins; stage 2) microaneurysm formation, mostly in the posterior pole; stage 3) arteriovenous anastomosis, usually in the peripapillary area; stage 4) ischemic complications such as retinal neovascularization, iris rubeosis, proliferative retinopathy, vitreous hemorrhage, and neovascular glaucoma (Figure 1).

Hypertensive retinopathy (HR) was classified according to the Wong-Mitchell system[31] (adopted retrospectively for study patients enrolled before 2004), in which "none" indicates no detectable signs; "mild" includes generalized arteriolar narrowing, focal arteriolar narrowing, arteriovenous nicking, opacity (copper wiring) of the arteriolar wall, or a combination thereof; "moderate" consists of retinal hemorrhages (blot-, dot-, or flame-shaped), microaneurysms, cotton wool spots, hard exudates, or a combination thereof; and "malignant" is characterized by signs of retinopathy and swelling of the optic disc (Figure 2).

Results

Of the 43 patients, 35 were female (81.4%), resulting in a F:M ratio of 4.4:1. The mean age at diagnosis was 32.6 years (range: 16–54 years) and the mean length of follow-up was 51 months

Table 1. Criteria for the classification of Takayasu arteritis[25].

Criterion	Definition
Age at onset ≤ 40 years	Development of symptoms or findings related to Takayasu arteritis at age ≤ 40 years
Claudication of the extremities	Development and worsening of fatigue and discomfort in muscles of one or more extremities while in use, especially the upper extremities
Decreased brachial artery pulse	Decreased pulsation of one or both brachial arteries
Blood pressure difference > 10 mmHg	Difference of > 10 mmHg in systolic blood pressure between arms
Bruit over subclavian arteries or aorta	Bruit audible on auscultation over one or both subclavian arteries or abdominal aorta
Arteriogram abnormality	Arteriographic narrowing or occlusion of the entire aorta, its primary branches, or large arteries in the proximal upper or lower extremities, not due to arteriosclerosis, fibromuscular dysplasia, or similar causes; changes usually focal or segmental

*For purposes of classification, a patient is assumed to have Takayasu arteritis if at least 3 of these 6 criteria are met. The presence of any 3 or more criteria has a sensitivity of 90.5% and a specificity of 97.8%.

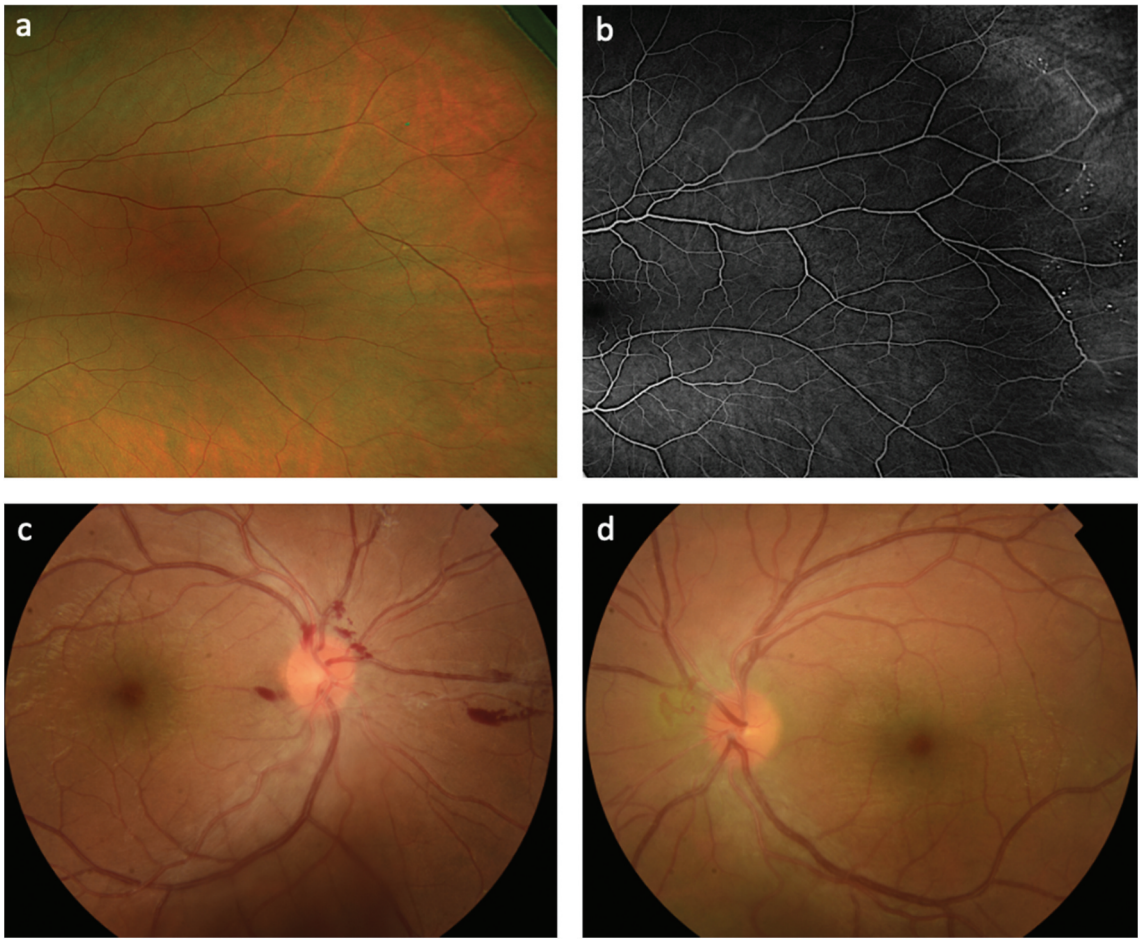

Figure 1. Color fundus photography (a) and fluorescein angiography (b) of the left eye show peripheral arteriovenous shunts and microaneurysms in the temporal side of peripheral retina in a patient with stage III Takayasu retinopathy. Color fundus photographs of the right eye (c) and the left eye (d) of a patient with stage IV Takayasu retinopathy. Both eyes show microaneurysms and ischemic complications (optic disc and retinal neovascularization) complicated by pre-retinal hemorrhages in the right eye.

(range: 9–84 months). The clinical, diagnostic, and therapeutic features of the whole cohort are reported elsewhere.[13] The focus of this study was the 16 TA patients (37.2%; 11 females and 5 males) in whom ocular manifestations were detected. The median latency in the diagnosis was 19 months (range: 9–27 months), with the longest diagnostic delay occurring in patients with predominant involvement of the abdominal aorta. The spectrum of chief complaints at presentation is summarized in Table 2. The angiographic classification of TA[26–28] was as follows: type I in 6 patients (37.5%), type IIa in 2 patients (12.5%), type IIb in 4 patients (25%), type III in 2 patients (12.5%), and type V in 2 patients (12.5%). No patient had type IV disease.

The number of patients with TR was slightly higher (9 out of 16 patients: 56.3%) than the number with HR (7 out of 16 patients: 43.7%). Among the 9 patients with TR, 15 eyes (83.3%) were affected. Stage 1, mostly consisting of dilation of the retinal veins, was diagnosed in 7 eyes (46.6%). Stage 2, characterized by capillary microaneurysms associated with an enhanced permeability of the vessel walls, consistently localized in the posterior pole, was present in 5 eyes (33.3%). Stage 3, in which arteriovenous anastomoses develop around the disc and in the peripapillary area and occur together with capillary non-perfusion areas, was determined in 2 eyes (13.3%). In the 1 (left) eye (6.7%) with stage 4 TR, retinal neovascularization and vitreous hemorrhages were detected whereas the other (right) eye, in which arteriovenous anastomoses were seen, was one of the 2 eyes with stage 3 TR (Table 2). The arm-to-retina circulation time was measured in 5 patients (10 eyes) with TR and was prolonged in all of them (mean 21.1 ± 7.7 s). Two patients (4 eyes) had a delayed arteriovenous filling time.

Among the 7 patients (14 eyes) with HR, the abnormalities were mild in 6 eyes (42.8%), consisting of generalized arteriolar narrowing in 2 eyes, focal arteriolar narrowing in 2 eyes, and arteriovenous nicking in the other 2 eyes. Moderate changes were detected in 6 eyes (42.8%) and included a heterogeneous array of variably shaped retinal hemorrhages, cotton wool spots, and microaneurysms. Finally, in 2 eyes (14.3%), clear signs of HR and swelling of the optic disc indicated malignant HR. For the purpose of comparison, Table 3 summarizes the most common abnormalities detected by FFA in the two groups of patients with TR and HR. Ocular ischemia is the obvious consequence of a reduced ocular blood flow caused by the restriction of the carotid artery. Interestingly, it has been reported that radial artery pulselessness can predict a reduced

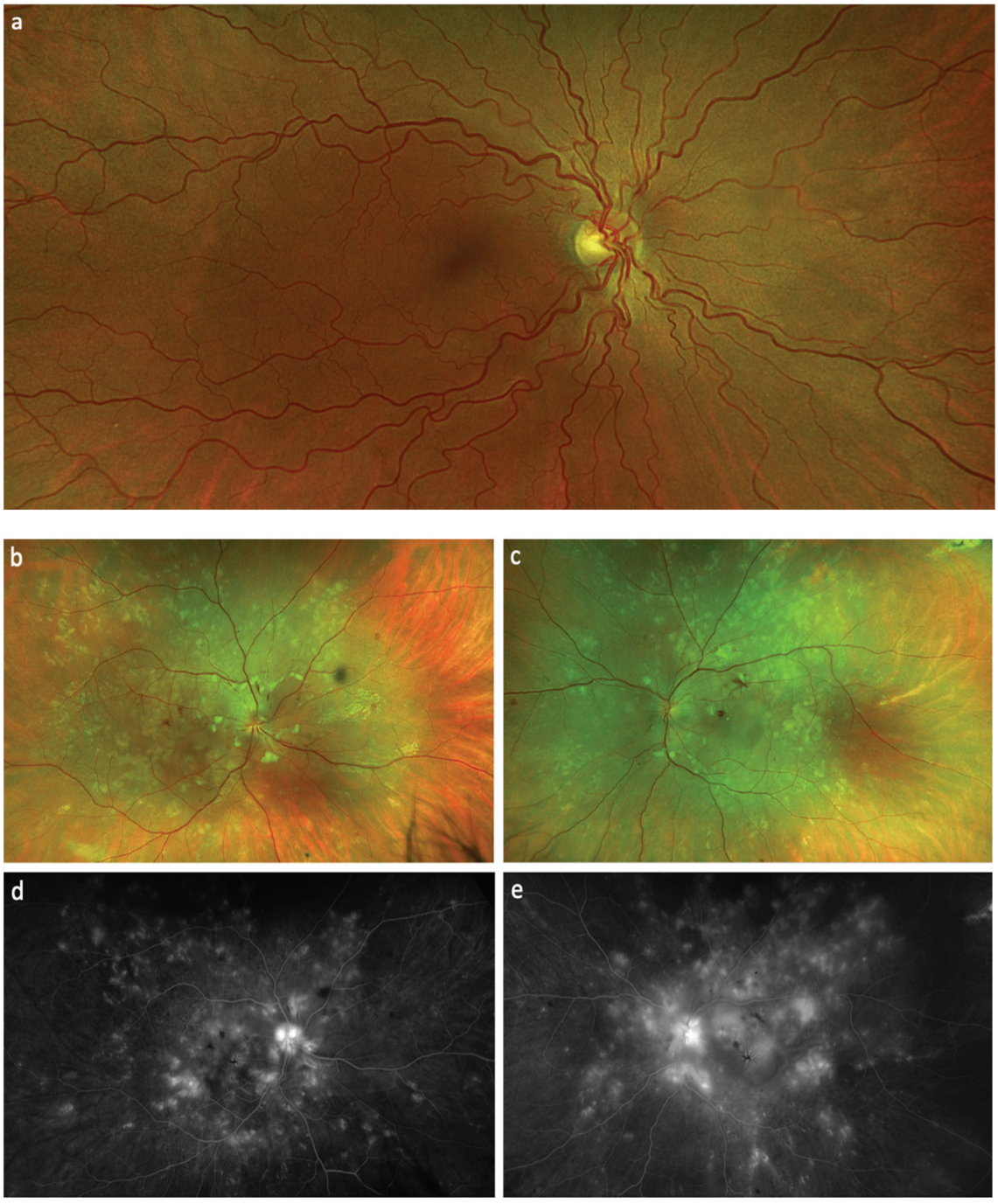

Figure 2. Ultra-wide field color fundus photography (a) of the right eye of a patient with mild hypertensive retinopathy. The image shows generalized arteriolar narrowing, arteriovenous nicking and marked vascular tortuosity. Ultra-wide field color fundus photographs of the right eye (b) and left eye (c) of a patient with malignant hypertensive chorioretinopathy show optic disc swelling, arteriolar narrowing, intraretinal hemorrhages, cotton wool spots and multiple focal lesions with yellowish halo (Elschnig spots). Fluorescein angiography of the right eye (d) and left eye (e) show optic disc leakage, cystoid macular edema with classic petaloid leakage pattern, blockage from intraretinal hemorrhages and cotton wool spots. In the mid-peripheral retina multiple patchy hyperfluorescent lesions correspond to damage of the outer retinal layers due to non-perfused areas of the underlying choriocapillaris.

perfusion of the ipsilateral eye.[32] In our cohort, 4 patients had absent or diminished pulses (Table 2), including 2 patients with radial artery pulselessness. As expected, signs of retinal hypoperfusion of the ipsilateral eye were recognized in both patients and were especially prominent in one of them.

OCT angiograms at diagnosis were available for 6 patients with TR and 3 with HR. In 2 (4 eyes) of the latter patients, the vascular architecture was only slightly altered. Twelve eyes of 7 patients showed a disruption of the perifoveal anastomotic capillary arcade, with a variable degree of rarefaction of the perifoveal vascular density in 5 of them. Capillary microaneurysms were detected in 7 eyes, vascular loops in 4 eyes, and an enlargement of the foveal avascular zone in both the superficial and deep capillary plexuses of 8 eyes of 6 patients. The average area of either capillary plexus was not calculated.

BCVA was slightly reduced (20/30) in 1 eye, severely reduced (from 20/40 to 20/200) in 13 eyes, reduced to no light perception in 1 eye, and to counting fingers and hand

Table 2. Basic epidemiological data, systemic manifestations and ocular findings at diagnoHsis in 16 patients with Takayasu arteritis.

Variables	Number (%)
Caucasian ethnicity	16 (100)
Sex (F/M)	11/5
Mean age at onset, years (range)	35.4 (18–54)
Median diagnostic delay, months	23 (9–33)
Mean length of follow-up, months (range)	46 (16–79)
Constitutional symptoms (persistently low fever, general ill feeling, night sweats, fatigue, anorexia, weight loss, arthralgias)	11/16 (68.7)
Vertigo/dizziness	5/16 (31.2)
Headache	5/16 (31.2)
Carotidynia/carotid bruits	2/16 (12.5)
Hypertension	7/16 (43.7)
Exertional syncope, exertional chest pain	3/16 (18.7)
Limb claudication	6/16 (37.5)
Absent or diminished pulses	4/16 (25.0)
Blood pressure discrepancies between limbs	4/16 (25.0)
Amaurosis fugax	4/16 (25.0)
Monocular/binocular blurred vision, floaters, reduction of visual acuity, metamorphopsia	9/16 (56.2)
Visual loss in one or both eyes	3/16 (18.7)
Takayasu retinopathy	9/16 (56.2)
Hypertensive retinopathy	7/16 (43.7)
Angiographic classification[26–28]	6/16 (37.5)
Type I	2/16 (12.5)
Type IIa	3/16 (18.8)
Type IIb	1/16 (6.2)
Type IIb (C+)	2/16 (12.5)
Type III	0/16
Type IV	2/16 (12.5)
Type V	
Takayasu retinopathy stage (eyes)[30]	3/18 (16.7)
Stage 0	7/18 (38.9)
Stage 1	5/18 (27.8)
Stage 2	2/18 (11.1)
Stage 3	1/18 (5.5)
Stage 4	
Hypertensive retinopathy grade[31]	3/7 (42.9)
Mild	3/7 (42.9)
Moderate	1/7 (14.2)
Malignant	

motion in 1 and 2 eyes, respectively (Table 4). Intra-ocular pressure was within the normal limits in all but the 4 eyes (12.5%) of 2 patients at the time of the first evaluation, but increased in 15 eyes (46.8%) of 9 patients at variable times during follow-up and was attributed to the protracted consumption of glucocorticoids (GC).

In the patient who presented with exudative retinal detachment and papilledema secondary to severe hypertension, following an extensive examination she was eventually diagnosed with TA. Ocular involvement was found in 11 patients at variable times (from 9 months to 4 years) during the first (6 patients) or second (5 patients) relapse of the disease, in step with the demonstration of an extension of the arterial involvement. However, ocular signs and symptoms were first detected in the remaining 4 patients when they were considered to have inactive disease. Two patients died of cerebral hemorrhage and myocardial infarction 3 and 5 years after the diagnosis, respectively.

Table 3. The most common abnormalities of fundus fluorescein angiography observed in 16 patients with Takayasu arteritis and ocular involvement.

Takayasu retinopathy 9 patients (15 eyes)
- Engorged retinal veins (4 eyes: 26.6%)
- Optic disc pallor (2 eyes: 13.3%)
- Narrowed retinal arteries (1 eye: 6.7%)
- Microaneurysms (5 eyes: 33.3%)
- Arteriovenous shunts or anastomoses (2 eyes: 13.3%)
- Retinal neovascularization (1 eye: 6.7%)

Hypertensive retinopathy 7 patients (14 eyes)
- Generalized arteriolar narrowing (2 eyes: 14.3%)
- Focal arteriolar narrowing (2 eyes: 14.3%)
- Arteriovenous nicking (2 eyes: 14.3%)
- Dot- or flame-shaped hemorrhages (3 eyes: 21.4%)
- Microaneurysms (1 eye: 7.1%)
- Cotton wool spots (2 eyes: 14.3%)
- Proliferative retinopathy (1 eye: 7.1%)
- Optic disc swelling (1 eye: 7.1%)

GC are considered the therapeutic cornerstone for remission induction in TA and were prescribed to all our patients. In one patient, given the persistence of high fever and the severity of the overall clinical picture according to the Indian Takayasu Activity Score (ITAS),[33] three intravenous pulses of methylprednisolone (1 g daily for 3 days) were initially given, followed by 0.5 mg of oral prednisone/kg/day plus 15 mg subcutaneous methotrexate weekly. Six months later, after the active phase of the disease had subsided, the patient underwent panretinal photocoagulation for optic disc neovascularization. In the remaining 15 patients, the starting daily oral dose of GC ranged from 0.5 to 1 mg/kg, depending on the ITAS assessment of disease activity. The initial dose was progressively tapered in step with the reduction of the inflammatory process.

An immunosuppressive or biologic agent was consistently added to the GC regimen both for its potential reduction of the cumulative GC dose and to reduce the risk of disease relapse.[3,8,10,12] Five patients received a daily dose of 2 mg azathioprine/kg and 2 patients a daily dose of 1.5 mg cyclophosphamide/kg. In addition to GC, 9 patients were given weekly subcutaneous injections of 15 mg methotrexate, including 3

Table 4. Endovascular procedures, best-corrected visual acuity before and after the intervention, ocular outcomes, and complications in 9 patients with Takayasu arteritis.

No.	Sex/ Age	Eyes	TR Stage/ HR Grade	Endovascular procedure	BCVA Before	BCVA After	Ocular outcomes	Post-operative course/Complications
1	F/46	OD	1	Graft replacement stent	20/40	20/40	Slight dilation of retinal veins in OD	Uneventful/None
		OS	0		20/40	20/40		
2	F/21	OD	1	Sequential (within one month) percutaneous endovascular stent implantation on both sides	20/40	20/20	Marked improvement of TR in both eyes	Uneventful/None
		OS	1		20/80	20/30		
3	F/36	OD	3	Angioplasty and stenting of the subclavian and carotid arteries	20/40	20/40	Improvement of arterio-venous anastomoses and proliferative retinopathy in OS	Symptomatic stenosis recurred 11 months later
		OS	4		20/60	20/40		
4	F/44	OD	2	Endovascular balloon angioplasty of the subclavian and carotid arteries	20/30	20/30	Decrease of arterio-venous anastomoses in OS.	Initially uneventful. Death 3 years after the diagnosis due to ictus
		OS	3		NLP	HM		
5	F/45	OD	Moderate	Graft replacement stent	HM	CF	Unchanged focal arteriolar narrowing	Symptomatic stenosis recurred 16 months later
		OS			CF	CF		
6	M/ 33	OD	Mild	Endovascular balloon angioplasty	20/200	20/200	Initial improvement of retinal hemorrhages in OS followed by NVG in both eyes	NVG was treated in another ophthalmology center. No further news available
		OS			20/200	20/120		
7	F/27	OD	Moderate	Open bypass grafting	HM	CF	Reduction of flame-shaped hemorrhages and cotton wool spots, more evident in OD	Uneventful/None. Death 5 years after the diagnosis due to myocardial infarction
		OS			20/200	20/200		
8	M/ 32	OD	Malignant	Surgical bypass of renal arteries	20/40	20/30	Bilateral decrease of disk swelling, arteriolar narrowing and intraretinal hemorrhages	Remarkable improvement of renovascular hypertension
		OS			20/40	20/20		
9	F/47	OD	Mild	Percutaneous transluminal angioplasty	20/40	20/40	Minor improvement of arteriolar narrowing in OS	Uneventful/None
		OS			20/120	20/60		

BCVA: best-corrected visual acuity; CF: counting fingers; HM: hand motion; HR: hypertensive retinopathy grading according to the Wong-Mitchell classification system[31]; NLP: no light perception; NVG: neovascular glaucoma; TR: Takayasu retinopathy staging according to Uyama & Asayama.[30]

patients with relapsing/refractory disease who were treated with GC in combination with the humanized anti-human IL-6 R antibody tocilizumab[34] at a dose of 4 mg/kg every 2 weeks for 3 months followed by every 4 weeks for another 3 months.

Overall remission was achieved in 14 patients (87.5%), including 11 in whom it was sustained (68.7%). The median time to remission was 4.8 months (3.7–9.4 months) and to sustained remission 23 months (14.3–29.2 months). One or more relapses were diagnosed in 7 patients (43.7%) at variable intervals during follow-up, corresponding to a median time of 6.6 months (4.5–16.3 months) between first remission and first relapse.

In TA, once the active phase has subsided and the disease enters a chronic obliterative phase, endovascular recanalization of the stenotic lesions becomes an important therapeutic objective, with the aim of improving the general symptoms and, for patients with ocular involvement, potentially recovering or improving visual acuity. Two patients underwent laser photocoagulation of the ischemic areas. Five patients did not undergo endovascular intervention because it was refused or they were lost to follow-up (3 and 2 patients, respectively). Information on the outcomes of recanalization of the involved arteries through reconstructive surgery or less invasive endovascular interventions, including angioplasty balloon or graft replacement stents, is incomplete because the procedures were carried out either by different vascular surgeons in our own university hospital or in extra-regional expert centers. Nine patients underwent patency procedures (Table 4); in 7, the procedure consisted of percutaneous transluminal angioplasty or a graft replacement stent, both of which are widely used to treat stenoses in short arterial segments. In the remaining 2 patients, with long segment stenosis or occlusion, especially of the renal arteries, open bypass was performed, consistent with the data in the literature.[3,12,35]

Following the recanalization procedure, BCVA was normal or slightly reduced in 5 eyes, remained unchanged in 6 eyes, and improved in 7 eyes. To reduce the risk of occlusion or restenosis, maintenance immunosuppression was continued after recanalization. The post-operative course was uneventful in 4 patients, whereas symptomatic stenosis and consequent visual symptoms recurred in 2 patients 11 and 16 months after the endovascular procedure. One patient developed neovascular glaucoma that was initially treated with panretinal photocoagulation but was later further treated and followed-up in the ophthalmic clinic of another city, with unknown outcome. A noteworthy, excellent result was obtained in a patient with malignant renovascular hypertension who underwent surgical bypass of the renal arteries, which resulted in normalization of the BCVA and a remarkable reduction of the blood pressure values.

While the first 7 patients, enrolled until 2010, were routinely given a 6-month course of daily anti-platelet therapy (aspirin 100 mg plus clopidogrel 75 mg), in the 9 subsequently enrolled patients this treatment was limited to those at risk of vascular ischemic complications, in accordance with the EULAR-endorsed recommendations.[35–37]

Discussion

Ocular manifestations are not a constant feature of TA; rather, their prevalence is variable, ranging, for example, from 33%[38] and 35%[39] in Japan, to 44.3%[22] in South Korea, and 38%[24] and 67%[40] in India. The extent to which genetic, geographic, and diagnostic factors account for the variations in the prevalence of this granulomatous large-vessel vasculitis remains to be established. A careful search of the literature indicates that, while the general topic "Takayasu arteritis" has so far been the subject of nearly 5,450 papers, with authors from all over the world, only 41 of the respective studies specifically addressed the ocular manifestations of TA (as of February 28, 2022). To the best of our knowledge, our study of 16 TA patients in Italy is the first ophthalmological study of a case series of TA.

As expected, involvement of the carotid artery and/or aortic arch was mainly seen in TR patients and it resulted in diminished flow of the internal carotid circulation, central retinal hypoperfusion, and a high prevalence of visual disturbances of variable severity. The different patterns of ischemic ocular manifestations, detected by fundus examination and, above all, by FFA (Table 3), were strictly related to the portion(s) of the carotid arteries that had become narrowed or occluded by the inflammatory granulomatous process, the overall duration of the ocular vascular failure, and the possible formation of a suitable vicarious blood supply to the involved eye(s). Similar findings have been described by other authors.[22–24] It is also worth emphasizing that OCT angiograms, according to the literature data[41,42] and our own experience, are an important imaging method to detect an enlargement of the foveal avascular zone and the occurrence of microvascular macular abnormalities in every phase of TR, even when no macular abnormalities are found on FFA.

Similarities and differences between the ocular findings in our patients and those reported in other studies are also worth emphasizing. In our cohort of 43 patients, TR was diagnosed in 9 (20.9%) and HR in 7 (16.3%) patients. Strikingly, in a study from Brazil that included 21 TA patients, all retinopathies were of the hypoperfusion type.[43] In older studies, carried out on 27 patients from India[40] and on 65 patients from Japan,[39] TR accounted for 33% and 33.8% of the cases whereas HR was diagnosed in 37% and 21.5%, respectively. More recently, the corresponding percentages were 22% and 16% in a cohort of 61 Indian patients.[24] and 62% and 33.9% in a cohort of 65 Turkish patients.[32] The latter study deserves special mention because the prevalence of TR was the lowest yet reported, which would seem to suggest a progressive decline in the occurrence of TR, presumably due to better imaging technologies and the consequent possibility of an earlier diagnosis. Another striking finding of the same study was the observation that all TR patients had stage 1 disease and none suffered visual loss following ischemic complications.[32]

Involvement of the thoracic and/or abdominal descending aorta, often associated with narrowing of one or both renal arteries, was mainly detected in the subset of TA patients with HR, whose clinical features were dominated by difficult-to-treat arterial hypertension while the carotids were usually spared. Generalized or focal arteriolar narrowing, papilledema,

variably shaped hemorrhages, and cotton wool spots in the macular area were the most frequently observed abnormalities in these patients. It is important to emphasize that these findings, and in particular papilledema, remarkably improved following the initiation of an effective anti-hypertensive therapy, thus providing indirect evidence that severe hypertension was responsible for their onset.

Ocular involvement was detected during the active phase of the disease in 12 patients, as the presenting feature in 1 patient, and in the course of the first or second relapse in the other 11 patients. In the remaining 4 patients in our cohort, ophthalmologic manifestations were first diagnosed when the disease was considered inactive. This discrepancy may be explained by the fact that there are no standardized and validated definitions of disease activity for large-vessel vasculitis, including TA.[3,33] An assessment based on the combination of clinical features, laboratory markers, and imaging data, proposed by Kerr et al. and Schmidt et al.[11,12] and adopted by our group (see the Material and Methods section), is not fully reliable and the results should therefore be interpreted with caution. Given the complexity and the usually relapsing-remitting course of TA, it is common to observe patients in whom, despite extended periods of clinically inactive disease, a progression of arterial damage can nonetheless be demonstrated by histopathologic examination of arterial biopsy specimens.[8,10,44]

Another point that merits discussion is the phase in which the ocular manifestations of TA become clinically apparent. Acute visual loss of variable severity, typical of anterior ischemic optic neuropathy, carries a worse prognosis, given that the recanalization procedure, often delayed until a precise diagnosis is made, usually results in the restoration of blood flow to the ischemic area but not necessarily in sight recovery. When the vascular narrowing follows a subacute or chronic course, ocular neovascularization yields better anatomic and functional results.[23]

Although no controlled studies have been published comparing open vs. endovascular revascularization, a better patency of the narrowed vessels is achieved after surgical bypass grafting than after percutaneous endovascular stenting, which is the less invasive procedure. While bypass surgery usually has a higher rate of severe post-operative complications,[45–47] endovascular treatment is associated with a significantly higher rate of restenosis (>50%) or occlusion of the reconstructed arteries.[45] In our experience, 2 out of the 7 patients (28.6%) who underwent endovascular stenting developed a restenosis, after 11 and 16 months, respectively. Of the 2 patients treated with open bypass, 1 had no complications and his renovascular hypertension greatly improved while the other had an uneventful post-operative course but died from myocardial infarction 5 years after the diagnosis.

None of our TA patients with ocular involvement had episcleritis/scleritis, which has been reported in a few cases of TA (reviewed in.[48]) Either condition can appear in patients in prolonged remission or, conversely, be the presenting manifestation of disease flare, with a unilateral or bilateral recurrent course. Scleritis may be a small-vessel manifestation of TA, but causality has not been proven.

A largely variable approach to the management of TA can be found in the literature in terms of GC dosage, the inclusion of disease-modifying, immunosuppressive or biologic agents, tapering modalities, validation of the clinical activity score, and a definition of a stable remission phase allowing a recanalization procedure.[3,10,49,50] This variability is related to the persistent mystery of the etiology of TA[12] and the lack of statistically sound, randomized clinical trials, both of which are a consequence of the relative rarity of the disease.[3] With the exception of the first 3 patients, who were diagnosed before 2004, the therapeutic strategy practiced by our group has followed the recommendations for the management of large-vessel vasculitis endorsed by the European League Against Rheumatism (EULAR), released in 2004[51] and updated in 2009[36] and 2020.[52]

Accordingly, our patients were prescribed GC soon after the diagnosis, to induce remission. After the achievement of disease control, the dose was slowly tapered to a target dose of 15 mg/day within 3 months and to 5–10 mg/day after 12 months. Disease-modifying agents, most frequently methotrexate, were administered in combination with GC, but there are as yet no controlled comparative studies demonstrating the greater efficacy of GC combined with methotrexate than with azathioprine or cyclophosphamide. The combination of GC with tocilizumab, an anti-IL-6 receptor monoclonal antibody, was reserved for 3 patients with relapsing/refractory disease.

Given the wide clinical heterogeneity of TA in terms of its presentation, progression, and therapeutic response as well as the safety of treatment, a timely diagnosis, effective and appropriate therapeutic measures, and close monitoring are of overarching importance to prevent ischemia and the consequent end-organ damage. To meet the multifaceted approaches to this complex disease, all patients with signs and symptoms suggestive of TA should be referred to highly specialized multidisciplinary teams that include specialists in internal medicine, rheumatology, clinical immunology, ophthalmology, and vascular surgery. This recommendation is also part of the latest EULAR guidelines.[52] Although the EULAR task force that updated the guidelines for the management of large-vessel vasculitis included a neuro-ophthalmologist among the 20 recommended clinical experts, it did not formulate a specific ophthalmologic principle. The ophthalmologist should play an important role in every phase of the disease to prevent or mitigate the potentially dreadful visual consequences of TA. The potential for hypoperfusive retinopathy in TA patients without ocular symptoms emphasizes the importance that these guidelines be implemented with new ophthalmologic perspectives.

The strengths of this study include: 1) the homogeneous collection of data, made possible through a carefully implemented collaboration between a tertiary eye-care center and a clinical immunology center of the same university hospital; 2) ophthalmological and clinical assessments made by the same ophthalmologists and the same internists, which reduced the risk of unwanted variability; and 3) the long follow-up, which exceeded 5 years in 7 of the 16 study patients (43.7%). However, several limitations to our study must also be acknowledged: 1) its retrospective nature; 2) the relatively small cohort of 16 patients, compared to the much larger numbers of patients recruited in polycenter or nationwide

epidemiological cohort studies[22,24,34,53]; 3) the incomplete retrieval of information related to biochemical features in the first 4 patients, enrolled between 2003 and 2005; 4) the incomplete imaging analysis during the course of the disease, as thorough examination and detailed imaging data were available for all patients only at presentation and when they were last seen; 5) the possibility that a wider and earlier use of biologic agents might have resulted in a lower rate of ocular involvement; and 6) recanalization of the involved arteries through reconstructive surgery or endovascular interventions carried out by different vascular surgeons.

Author contributions

RD, GA and FD conceived and designed the study, retrieved, collected and had full access to all the data in the study, and take responsibility for the integrity of the data and the accuracy of the analysis. RD wrote the manuscript. LC and LDS revised the manuscript for important intellectual content and supplied additional images of Takayasu arteritis. All authors reviewed the manuscript, approved the draft submission, and accept responsibility for all aspects of this study.

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ORCID

Luca Cimino MD http://orcid.org/0000-0001-7956-9950
Luca De Simone MD http://orcid.org/0000-0003-1471-1914

References

1. Lupi-Herrera E, Sánchez-Torres G, Marcushamer J, Mispireta J, Horwitz S, Vela JE. Takayasu's arteritis. Clinical study of 107 cases. *Am Heart J*. 1977;93(1):94–103. doi:10.1016/S0002-8703(77)80178-6.
2. Richards BL, March L, Gabriel SE. Epidemiology of large-vessel vasculidities. *Best Pract Res Clin Rheumatol*. 2010;24(6):871–883. doi:10.1016/j.berh.2010.10.008.
3. Kim ESH, Beckman J. Takayasu arteritis: challenges in diagnosis and management. *Heart*. 2018;104(7):558–565. doi:10.1136/heartjnl-2016-310848.
4. Tomelleri A, Campochiaro C, Sartorelli S, et al. Gender differences in clinical presentation and vascular pattern in patients with Takayasu arteritis. *Scand J Rheumatol*. 2019;48(6):482–490. doi:10.1080/03009742.2019.1581838.
5. Vautier M, Dupont A, de Boysson H, et al. Prognosis of large vessel involvement in large vessel vasculitis. *J Autoimmun*. 2020. 108:102419. doi:10.1016/j.jaut.2020.102419. Epub 2020 Feb 5.
6. Jennette JC, Falk RJ, Bacon PA, et al. 2012 revised International Chapel Hill consensus conference nomenclature of vasculitides. *Arthritis Rheum*. 2013;65(1):1–11. doi:10.1002/art.37715.
7. Numano F, Okawara M, Inomata H, Kobayashi Y. Takayasu's arteritis. *Lancet*. 2000;356(9234):1023–1025. doi:10.1016/S0140-6736(00)02701-X.
8. Schmidt J, Kermani TA, Bacani AK, et al. Diagnostic features, treatment, and outcomes of Takayasu arteritis in a US cohort of 126 patients. *Mayo Clin Proc*. 2013;88(8):822–830. doi:10.1016/j.mayocp.2013.04.025.
9. Seyahi E. Takayasu arteritis: an update. *Curr Opin Rheumatol*. 2017;29(1):51–56. doi:10.1097/BOR.0000000000000343.
10. Zaldivar Villon MLF, de la Rocha JAL, Espinoza LR. Takayasu Arteritis: recent developments. *Curr Rheumatol Rep* 2019 18;21 (9):45. doi:10.1007/s11926-019-0848-3.
11. Mason JC. Takayasu arteritis–advances in diagnosis and management. *Nat Rev Rheumatol*. 2010;6(7):406–415. doi:10.1038/nrrheum.2010.82.
12. Serra R, Butrico L, Fugetto F, et al. Updates in pathophysiology, diagnosis and management of takayasu arteritis. *Ann Vasc Surg*. 2016;35:210–225. doi:10.1016/j.avsg.2016.02.011.
13. Dammacco F, Cirulli A, Simeone A, et al. Takayasu arteritis: a cohort of Italian patients and recent pathogenetic and therapeutic advances. *Clin Exp Med*. 2021;21(1):49–62. doi:10.1007/s10238-020-00668-7.
14. Elizalde J, Capella MJ. Takayasu's retinopathy. *Int Ophthalmol*. 2011;31(6):533–537. doi:10.1007/s10792-011-9500-6.
15. Sakthiswary R, Syazarina SO, Shaharir SS, Said MS, Hanom F. Blindness in a pulseless young woman: lessons learned. *Ocul Immunol Inflamm*. 2012;20(4):309–311. doi:10.3109/09273948.2012.690491.
16. Shailaja S, Vivek G, Shetty R, Kamath Y. 'Eye is a window to the pulse': bilateral ocular ischaemic syndrome as a presenting manifestation of Takayasu arteritis. *BMJ Case Rep*. 2013 Apr 29;2013. (pii: bcr2013009461). doi:10.1136/bcr-2013-009461.
17. Lee JC, Wang MY, Damodar D, Sadun AA, Sadda S. Headache and whiteout vision as the presenting symptoms in a case of Takayasu retinopathy. *Retin Cases Brief Rep*. 2014;8(4):273–275. doi:10.1097/ICB.0000000000000091.
18. Mashru P, Sagdeo P, Gattimallanahali Y, Mangat G. Atypical eye complication in Takayasu's arteritis. *BMJ Case Rep*. 2016;2016: pii: bcr2016215018. doi:10.1136/bcr-2016-215018.
19. Babu K, Parameswarappa DC. Atypical tolosa hunt syndrome with bilateral sclerokeratitis and optic atrophy in Takayasu's arteritis. *Am J Ophthalmol Case Rep*. 2017;5:41–43. doi:10.1016/j.ajoc.2016.11.006.
20. Pallangyo P, Epafra E, Nicholaus P, Lyimo F, Kazahura P, Janabi M. Bilateral ocular ischemia-induced blindness as a presenting manifestation of Takayasu arteritis: a case report. *J Med Case Rep*. 2017;11(1):153. doi:10.1186/s13256-017-1330-3.
21. Gupta V, Luthra S, Shrinkhal N, Sinha S. Takayasu's arteritis: a unique ophthalmic presentation with CRAO and BRVO. *BMJ Case Rep*. 2019;12(8):ii: e228909. doi:10.1136/bcr-2018-228909.
22. Chun YS, Park SJ, Park IK, Chung H, Lee J. The clinical and ocular manifestations of Takayasu arteritis. *Retina*. 2001;21 (2):132–140. doi:10.1097/00006982-200104000-00006.
23. Peter J, David S, Joseph G, Horo S, Danda D. Hypoperfusive and hypertensive ocular manifestations in Takayasu arteritis. *Clin Ophthalmol*. 2010;4:1173–1176. doi:10.2147/OPTH.S12331.
24. Peter J, David S, Danda D, Peter JV, Horo S, Joseph G. Ocular manifestations of Takayasu arteritis: a cross-sectional study. *Retina*. 2011;31(6):1170–1178. doi:10.1097/IAE.0b013e3181fe540b.
25. Arend WP, Michel BA, Bloch DA, et al. The American college of rheumatology 1990 criteria for the classification of Takayasu arteritis. *Arthritis Rheum*. 1990;33(8):1129–1134. doi:10.1002/art.1780330811.
26. Hata A, Noda M, Moriwaki R, Numano F. Angiographic findings of Takayasu arteritis: new classification. *Int J Cardiol*. 1996;54:Suppl:S15563. doi:10.1016/S0167-5273(96)02813-6.
27. Moriwaki R, Noda M, Yajima M, Sharma BK, Numano F. Clinical manifestations of Takayasu arteritis in India and Japan–new classification of angiographic findings. *Angiology*. 1997;48(5):369–379. doi:10.1177/000331979704800501.

28. Nastri MV, Baptista LP, Baroni RH, et al. Gadolinium-enhanced three-dimensional MR angiography of Takayasu arteritis. *Radiographics*. 2004;24(3):773–786. doi:10.1148/rg.243035096.
29. Kerr GS, Hallahan CW, Giordano J, et al. Takayasu arteritis. *Ann Intern Med*. 1994;120(11):919–929. doi:10.7326/0003-4819-120-11-199406010-00004.
30. Uyama M, Asayama K. Retinal vascular changes in Takayasu's disease (pulseless disease), occurrence and evolution of the lesions. *Doc Ophthalmol Proc Series*. 1976;9:549–554.
31. Wong TY, Mitchell P. Hypertensive retinopathy. *N Engl J Med*. 2004;351(22):2310–2317. doi:10.1056/NEJMra032865.
32. Esen F, Ergelen R, Alibaz-Öner F, Çelik G, Direskeneli H, Kazokoğlu H. Ocular findings and blood flow in patients with Takayasu arteritis: a cross-sectional study. *Br J Ophthalmol*. 2019;103(7):928–932. doi:10.1136/bjophthalmol-2018-312580.
33. Misra R, Danda D, Rajappa SM, et al. Development and initial validation of the Indian Takayasu Clinical Activity Score (ITAS2010). *Rheumatology*. 2013;52(10):1795–1801. doi:10.1093/rheumatology/ket128.
34. Nakaoka Y, Isobe M, Tanaka Y, et al. Long-term efficacy and safety of tocilizumab in refractory Takayasu arteritis: final results of the randomized controlled phase 3 TAKT study. *Rheumatology (Oxford)*; 2020 Jan 17. 59(9): 2427–2434. pii: kez630. doi: 10.1093/rheumatology/kez630. [Epub ahead of print].
35. Saadoun D, Lambert M, Mirault T, et al. Retrospective analysis of surgery versus endovascular intervention in Takayasu arteritis: a multicenter experience. *Circulation*. 2012;125(6):813–819. doi:10.1161/CIRCULATIONAHA.111.058032.
36. European Vasculitis Study Group, Mukhtyar C, Guillevin L, Cid MC, et al. EULAR recommendations for the management of large vessel vasculitis. *Ann Rheum Dis*. 2009;68(3):318–323. doi:10.1136/ard.2008.088351.
37. de Souza AW, Machado NP, Pereira VM, et al. Antiplatelet therapy for the prevention of arterial ischemic events in Takayasu arteritis. *Circ J*. 2010;74(6):1236–1241. doi:10.1253/circj.CJ-09-0905.
38. Baba T, Itakura K, Tanaka R, Kawasaki T, Kiyosawa M, Numano F. Importance of fluorescein angiographic study in evaluating early retinal changes in Takayasu disease. *Jpn J Ophthalmol*. 1999;43(6):546–552. doi:10.1016/S0021-5155(99)00110-0.
39. Kiyosawa M, Baba T. Ophthalmological findings in patients with Takayasu disease. *Int J Cardiol*. 1998;66(Suppl 1):S141–S147. doi:10.1016/S0167-5273(98)00162-4.
40. Sagar S, Kar S, Gupta A, Sharma BK. Ocular changes in Takayasu's arteritis in India. *Jpn J Ophthalmol*. 1994;38:97–102.
41. Chotard G, Diwo E, Coscas F, Butel N, Saadoun D, Bodaghi B. Fluorescein and OCT angiography features of Takayasu disease. *Ocul Immunol Inflamm*. 2019;27(5):774–780. doi:10.1080/09273948.2018.1455876.
42. Zeng Y, Duan J, Ge G, Zhang M. Therapeutic management of ocular ischemia in Takayasu's arteritis: a case-based systematic review. *Front Immunol*. 2022;12:791278. doi:10.3389/fimmu.2021.791278.
43. Matos KT, Arantes T, Souza AW, Ramos MH, Allemann N, Muccioli C. Retinal angiography and colour Doppler of retrobulbar vessels in Takayasu arteritis. *Can J Ophthalmol*. 2014;49(1):80–86. doi:10.1016/j.jcjo.2013.09.014.
44. Aydin SZ, Direskeneli H, Merkel PA. International Delphi on disease activity assessment in large-vessel vasculitis. assessment of disease activity in large-vessel vasculitis: results of an international delphi exercise. *J Rheumatol*. 2017;44(12):1928–1932. doi:10.3899/jrheum.161269.
45. Kim YW, Kim DI, Park YJ, et al. Surgical bypass vs endovascular treatment for patients with supra-aortic arterial occlusive disease due to Takayasu arteritis. *J Vasc Surg*. 2012;55(3):693–700. doi:10.1016/j.jvs.2011.09.051.
46. Lee GY, Jeon P, Do YS, et al. Comparison of outcomes between endovascular treatment and bypass surgery in Takayasu arteritis. *Scand J Rheumatol*. 2014;43(2):153–161. doi:10.3109/03009742.2013.822096.
47. Dogra M, Kumar A, Bajgai P, et al. Outcome of endovascular procedures on ocular findings in Takayasu arteritis. *Retina*. 2019;39(6):1142–1148. doi:10.1097/IAE.0000000000002103.
48. Sureja NP, Kalyan S, Patel MR. Recurrent scleritis as a presenting manifestation of asymptomatic occult Takayasu arteritis. *Rheumatol Adv Pract*. Nov 28, 2020;5(1):rkaa065. doi:10.1093/rap/rkaa065.
49. Campochiaro C, Tomelleri A, Sartorelli S, et al. Drug retention and discontinuation reasons between seven biologics in patients with Takayasu arteritis. *Semin Arthritis Rheum*; 2020 Jan 25. 50(3): 509–514. pii: S0049-0172(20)30005-6. doi: 10.1016/j.semarthrit.2020.01.005. [Epub ahead of print]
50. Mutoh T, Shirai T, Fujii H, Ishii T, Harigae H. Insufficient use of corticosteroids without immunosuppressants results in higher relapse rates in Takayasu arteritis. *J Rheumatol*. 2020 Feb;47(2):255–263. doi:10.3899/jrheum.181219. Epub 2019 May 15.
51. Dougados M, Betteridge N, Burmester GR, et al. EULAR standardised operating procedures for the elaboration, evaluation, dissemination, and implementation of recommendations endorsed by the EULAR standing committees. *Ann Rheum Dis*. 2004;63(9):1172–1176. doi:10.1136/ard.2004.023697.
52. Hellmich B, Agueda A, Monti S, et al. 2018 Update of the EULAR recommendations for the management of large vessel vasculitis. *Ann Rheum Dis*. 2020;79(1):19–30. doi:10.1136/annrheumdis-2019-215672.
53. Watanabe Y, Miyata T, Tanemoto K. Current clinical features of new patients with Takayasu arteritis observed from cross-country research in Japan: age and sex specificity. *Circulation* 2015 3;132(18):1701–1709. doi:10.1161/CIRCULATIONAHA.114.012547.